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The prognosis of HPV-associated metastatic pharyngeal patients by primary and distant site

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Abstract

Objectives: Human papillomavirus (HPV) positivity is a favorable prognostic factor in the general population of head and neck squamous cell carcinoma (HNSCC) patients. However, its impact on the survival of metastatic HNSCC of pharynx (mHNSC-P) patients is unclear. This study aims to investigate the associations between HPV status and survival in mHNSC-P patients.

Methods: 735 mHNSC-P patients diagnosed at first presentation from 2010 to 2016 were retrieved from the Surveillance, Epidemiology and End Result database (SEER). Chi-Squared test, univariate and multivariate cox proportional hazards model, Kaplan–Meier analysis, and log-rank test were applied to compare HPV-positive and -negative mHNSC-P patients.

Result: Using univariate cox proportional hazards analysis, HPV status, primary site, T stage, treatment and distant metastatic site correlate with the overall survival (OS) and disease-specific survival (DSS) in mHNSC-P patients. Multivariate cox regression analysis shows that HPV-positive mHNSC-P patients experienced significantly better OS (HR: 0.62 CI: 0.51–0.76, $p < 0.001$) and DSS (HR: 0.73 CI: 0.58–0.91, $p < 0.01$) as compared to HPV-negative mHNSC-P patients. Subgroup analysis indicates that HPV-associated OS and DSS benefits exist in patients with metastatic HNSCC of oropharynx (mHNSC-OP) but not in patients with metastatic HNSCC of non-oropharynx (mHNSC-non-OP). Among mHNSC-OP patients, HPV positivity confers disease-specific survival benefit in patients with oligometastatic rather than polymetastatic

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2021.105675.

patients. Furthermore, HPV associated OS and DSS advantages in mHNSC-OP with lung metastasis was observed.

Conclusion: HPV-positive mHNSC-OP patients with lung metastasis show better survival than HPV-negative mHNSC-OP patients, providing key information to guide patient treatment approaches.

Keywords

Human papillomavirus associated head and neck squamous cell carcinoma; The Surveillance, Epidemiology and End Result database; Overall survival; Disease-specific survival, metastatic head and neck squamous cell carcinoma of pharynx; Oropharyngeal squamous cell carcinoma; Non-oropharyngeal pharyngeal squamous cell carcinoma; Lung metastasis; Bone metastasis

Introduction

Head and neck squamous cell carcinoma (HNSCC) is a heterogeneous group of malignancies that arise in the mucosal epithelium of the oral cavity, oropharynx, hypopharynx, and larynx [1]. Approximately 890,000 new cases are diagnosed worldwide, and 430,000 deaths occur annually [2]. The prevalence of HNSCC is geographically variable; carcinogen-driven HNSCC is common among patients from Asia and Australia, whereas HPV infection now accounts for a significant percentage of HNSCC cases in the USA and western Europe with a continued rise in prevalence [3–5].

HPV-positive HNSCC differs from HPV-negative HNSCC in epidemiological, etiological, biological, and clinical presentations [6]. HPV infection causes around 70% of oropharyngeal squamous cell carcinoma (OPSCC) and a small percentage of cancers from non-oropharyngeal anatomical sites, including 25% of larynx and hypopharynx and 3% of the oral cavity [7]. The tumor cell of HPV-positive HNSCC tends to spread to the cervical lymph node at a relatively early T stage [8]. Notably, HPV-positive OPSCC patients with cervical lymph node metastases have better survival outcomes than HPV-negative OPSCC patients [9]. In addition to cervical lymph node involvement, around 15% of HPV-positive OPSCC patients can also develop distant metastasis [10,11], even though numerous studies consistently show that HPV positivity is a well-known favorable prognosis indicator for a general HNSCC patient [1,12]. There are very few studies examining the relationship between HPV positivity and survival of patients with metastatic HNSCC. The importance of knowing the association of HPV positivity with prognosis in late stage HNSCC patients with distant metastases can be of tremendous benefit in patient consulting as well as clinical trial design since new trials would more likely enroll late stage HNSCC patients with metastases rather than early stage HNSCC patients.

Currently, there are very few studies that value HPV positivity in relation to survival of metastatic HNSCC of oropharynx (mHNSC-OP) patients [13–16]. No statistical survival difference between the recurrent/metastatic HPV-positive and HPV-negative HNSCC patients [17], however, this study is underpowered due to its very small sample size. The role of HPV positivity in metastatic HNSCC patients, especially in metastatic HNSCC of non-oropharynx (mHNSC-non-OP) patients require more confirmatory investigations.

In this study, a cohort of HNSCC patients retrieved from the Surveillance, Epidemiology and End Result database (SEER), which collects U.S. nationwide cancer cases, was used for analysis to avoid small sample size, single institute limitations, and provide sufficient cases for further sub-grouped analysis. Patient cohort used for analysis was narrowed down to metastatic oropharyngeal cancer and non-oropharyngeal cancer cases. Our results show a survival advantage in overall survival (OS) and disease-specific survival (DSS) in HPV-positive mHNSC-OP compared to HPV-negative mHNSC-OP and no evidence to confirm the survival benefits from HPV positivity in mHNSC-non-OP patients, providing physicians clues in patients consultant and therapy discussions.

Patients and methods

Study population

The National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database (http://seer.cancer.gov) recording the morbidity, mortality, and disease status of millions of cancer patients in the United States, was used for in this study. We retrieved 40,866 cases from SEER*Stat Database: Incidence - SEER 18 Regs Custom Data Head and Neck (select schemas with HPV recode and additional treatment fields), Nov 2018 Sub (2010–2016) by selecting Site and Morphology. Site recode ICD-O-3/WHO 2008 = ‘Oral Cavity and Pharynx’, ‘Tongue’, ‘Gum and Other Mouth’, ‘Nasopharynx’, ‘Tonsil’, ‘Oropharynx’, ‘Hypopharynx’, or ‘Other Oral Cavity and Pharynx’. We narrowed down the HSNCC cases to a 735-patient cohort that was used in this study after fulfilling the following criteria: 1) with distant metastases (M1 for patients diagnosed with the 7th derived AJCC M stage); 2) confirmed HPV status are available. The detailed ICD-O-3 site codes were summarized in supplementary Table 1. Only pharyngeal cancers were included after above selections. Metastatic site was identified under variables of “SEER Combined Mets at DX-bone (2010+)”, “SEER Combined Mets at DX-liver (2010+)”, “SEER Combined Mets at DX-lung (2010+)”, “CS mets at dx (2004–2015)”, “Mets at DX-Distant LN (2016+)” and “Mets at DX-Other (2016+)”.

Patient characteristics

All patients were divided into two groups: HPV-negative and HPV-positive. The clinical characteristics obtained from the database were: age of diagnosis (age was divided into ≤62 years old and >62 years old.), sex, race, primary site, tumor grade, T stage, N classification, insurance, marital status, treatment, and distant metastatic sites which included bone, brain, liver, and lung. We recorded the number of metastatic sites and classified it as single or multiple organ metastasis. The median OS follow-up was 19 months (range: 17–23 months) versus 10 months (range: 9–12 months) in the HPV-positive group and HPV-negative group, respectively. The median DSS follow-up was 23 months (range: 18–32 months) versus 15 months (range: 12–17 months) in the HPV-positive group and HPV-negative group, respectively.

Statistical analysis

The Chi-squared test or Fisher’s exact test was used to compare the difference between HPV-positive and HPV-negative groups. The one-year, two-year, and three-year OS and DSS

of HNSCC patients were compared using Kaplan–Meier analysis and log-rank test. The univariate and multivariate Cox proportional hazard regression models were performed to calculate the hazard ratio (HR) of death and were used to determine independent factors that may affect prognosis. A two-sided p-value < 0.05 was considered statistically significant. All analyses were performed using R software (Version 4.0.3, https://www.rproject.org/).

Results

Demographics of the cohort

The patient cohort used for analysis consisted of 735 metastatic HNSCC of pharynx (mHNSC-P) patients with 392 HPV-negative (53.3%) and 343 HPV-positive (46.7%) cases. The different clinical features among patient cohort are summarized in Table 1. Majority of patients (552 of 735) have oropharynx carcinoma. Median age is 62 years old. Briefly, there are more male, white, advanced N-stage, and married status patients in HPV-positive group than HPV-negative group.

HPV positivity correlates with better survival in metastatic HNSCC-P patients

The univariate cox proportional hazards analyses of potential predictors for the OS and DSS in metastatic HNSCC patients are shown in Table 2. Primary site, HPV status, T stage, treatment, bone metastasis, lung metastasis and brain metastasis were significantly associated with both OS and DSS ($p < 0.05$). Meanwhile, grade I-II and separated marital status were associated with worse OS ($p < 0.05$), while N2-N3 and uninsured status were associated with worse DSS ($p < 0.05$).

After adjusting for age, race, gender, grade, T stage, N stage and treatment by multivariate cox proportional hazard model, HPV-positive mHNSC-P patients still had better OS and DSS compared to HPV-negative mHNSC-P patients ($p < 0.05$). As shown in Fig. 1, mHNSC-P patients with HPV-positive status are more likely to have better OS and DSS than patients with HPV-negative status (OS: aHR: 0.62, 95 %CI: 0.51–0.76, $p < 0.001$; DSS: aHR: 0.73, 95 %CI:0.58–0.91, $p < 0.01$). The 1-year, 2-year and 3-year OS rates were 63.6%, 41.0% and 30.1% versus 42.9%, 24.5% and 19.2% in the HPV-positive patients and HPV-negative patients, respectively. In addition, the 1-year, 2-year and 3-year DSS rates of HPV-positive patients and HPV-negative patients were 68.3%, 49.2% and 38.1% versus 54.8%, 38.6% and 31.5%.

The HPV-positive associated survival benefit occurs in metastatic oropharyngeal cancer rather than metastatic non-oropharyngeal cancer

Due to the skewed numbers of oropharyngeal cancer vs non-oropharyngeal cancer in our patient cohort, we applied subgroup analysis by splitting the cohort into mHNSC-OP and mHNSC-non-OP. As shown in Fig. 2A and 2B, HPV-positive mHNSC-OP patients had significantly better OS ($p < 0.0001$) and DSS ($p < 0.01$) than HPV-negative mHNSC-OP patients. The DSS rate after 1-year, 2-year and 3-year in HPV-positive patients were 69.6%, 51.3% and 39.1% compared with 49.7%, 37.7%, and 31.6% for HPV-negative patients respectively. However, there was no significant survival difference observed between

HPV-positive and HPV-negative mHNSC-non-OP patients, including nasopharyngeal and hypopharyngeal cancers (Fig. 2C–F).

The HPV positivity associated survival benefit differs between OPSCC patients with oligo and ploymetastatic sites

HPV-positive mHNSC-OP patients had better OS and DSS than HPV-negative counterparts when only the oligometastatic organ was involved ($p < 0.05$, Fig. 3A–B). As for the polymetastatic OPSCC patients, HPV-positive patients seem to have better OS and DSS rates than HPV-negative counterparts (Fig. 3C–D, log-rank $p < 0.05$). However, after adjusting for T, N, age, gender, race and treatment, the adjusted HR for DSS is 0.84 with 95 %CI (0.6–1.15) ($p = 0.3$), indicating no survival benefit in HPV positivity in polymetastatic OPSCC patients.

To investigate the association of survival with the specific metastatic site, patients were grouped accordingly based on presence of lung and bone metastases (patients with liver and brain metastases were not analyzed due to small sample size). The HPV-positive mHNSC-OP patients with lung metastasis had significantly better DSS (aHR:0.04, 95 % CI 0.002–0.55, $p = 0.017$; Fig. 4A) and OS (aHR:0.02, 95 %CI: 0.002–0.33, $p = 0.006$; Supplementary Fig. 1) compared to HPV-negative patients. In contrast, there was no observed significant difference in DSS between HPV-positive and -negative mHNSC-OP patients with bone metastasis (aHR: 0.04, 95 %CI:0.0007–2.4, p =0.12, Fig. 4B).

Discussion

The association of HPV positivity with the survival of head and neck cancer patients has been investigated for more than a decade and numerous studies have shown that HPV-positive HNSCCs are distinct from HPV-negative HNSCC in terms of survival and biology. However, majority of these studies consisted of a large proportion of locoregionally advanced HNSCC therefore do not provide sufficient information to address potential correlation between HPV positivity and survival benefit in metastatic HNSCC. Here, we show that HPV-association is an independently favorable indicator of survival in 735 metastatic HNSCC patients. These findings contrast with results shown by Morris et al., which analyzed 35 cases of metastatic and 18 local/regional cases of HNSCC, where HPV-positive HNSCC did not have improved survival benefit compared to HPV-negative HNSCC [17]. The small sample size (only 53 patients in total) and the inclusion of local regional cases in this study may limit the survival difference to reach statistical significance. Because clinical trial recruitment usually involves metastatic cancer patients, the effect of HPV positivity on metastatic HNSCC patients' survival should be considered during patient consultant and clinical trial.

In this study, we observed that HPV positivity resulted in survival benefit for metastatic HNSCC patients specifically with oropharyngeal cancer. This finding is consistent with previous studies showing that HPV-positive metastatic oropharyngeal cancer is likely to survive longer than their HPV-negative counterparts [13,14]. Our study here makes the conclusion from the previous studies more robust by a relative bigger number of patients. Additionally, this is the first investigation based on the U.S. nationwide dataset to describe

that there is no observed survival benefit between HPV-positive and -negative mHNSC-non-OP patients, which consists with a study from The Danish Head and Neck Cancer Group displaying no different outcomes between HPV-positive and -negative non-OPSCC patients [18]. Although Chung et al. found the p16-positive non-oropharyngeal cancer patients have a significantly better outcome than the p16-negative non-oropharyngeal cancer patients [19], we should be aware that majority of their cases are locally advanced stage, which cannot be directly compared to metastatic patients in our study.

Here, we show that the outcome benefit for metastatic HPV associated HNSCCs is limited to the oropharyngeal site. This may indicate that the rejection of virus-related cancer cell requires a unique tumor immune environment. Single-cell RNA sequencing analysis on HPV associated HNSCC show that HPV-positive oropharyngeal cancer displays a divergent spectrum of helper CD4 + T cells and B cells [20]. Non-oropharyngeal mucosa may not have enough infiltrating immune cells to kill tumor cells loaded with viral antigens. Furthermore, the oncogenesis activated by HPV virus may accelerate tumor growth and invasion since not enough ejections of immune killings in non-oropharyngeal mucosa. Regardless of HPV status, the survival outcomes of different sub-anatomical HNSCCs show huge differences [21], which is consistent with our notion of tumor subsite's effect in HNSCCs. The sub-anatomic site to some extent determines the outcomes of host immune-virus interactions coordinating with findings shown in preclinical mouse model where HPV-positive tumors are significantly sensitive to anti-PD1 treatment when implanted in base of tongue compared to the flank [22]. Taken together, HPV status and primary tumor site should be considered as key factors in patient consultant and trial design for metastatic HNSCCs.

The metastatic OPSCCs were classified into oligometastatic OPSCC (single metastatic site) and polymetastatic OPSCC (multiple metastatic sites) [23]. A recent study by Saiyed et al. indicate a survival advantage in oligometastatic OPSCC compared to polymetastatic OPSCC [24], however, this is not a HPV associated study. Here, we show that there is significantly better prognosis for HPV-positive oligometastatic OPSCC than their HPV-negative counterparts, but there was no survival benefit if patients developed polymetastasis. In agreement with previous studies [13,14,25], we show that the OPSCC metastases are located preferentially in lung (52% and 47% for HPV-positive and HPV-negative), followed by bone (26% and 25% for HPV-positive and HPV-negative) and liver (14% and 13% for HPV-positive and HPV-negative). Furthermore, when comparing different oligometastatic sites, lung metastasis is the only site reaching statistical significance in DSS when comparing HPV-positive oligometastatic OPSCC with their HPV-negative counterparts. The mechanism underlying this finding is still poorly understood, but maybe involved with host immunity. An immune analysis on metastatic organs showed that the samples from metastatic cancer in lung have a higher immunogenic cell infiltrates than the samples from other metastatic sites including liver and bone [26]. And emerging studies indicate that cancer metastasize to liver could result in the systemic suppression of antitumor immunity by the coordinated activation of regulatory T cells and modulation of intratumoral CD11b + monocytes [27,28]. Bone marrow is a primary hematopoietic organ and a common site of cancer metastasis in breast, prostate, lung and head and neck cancers [29]. Specific cellular and molecular niches in the bone marrow with metastatic cancer may include high levels

of Treg cells and myeloid-derived suppressor cells (MDSCs) [30], which could lead to systemic immunosuppression.

There are some limitations of this study that should be acknowledged. Despite being retrospective, our study provides a comprehensive and large cohort size that limited by the nature of SEER data and may contain inherent bias. Furthermore, samples in SEER dataset lack HPV information on metastatic oral cavity and laryngeal cancers. The small number of HPV-positive metastatic non-oropharyngeal cancer patients (nasopharyngeal cancer, n = 101; hypopharyngeal cancer, n = 82) analyzed in this study may not be enough to make a definitive conclusion. Currently, we do not have enough evidence to exclude a possible minimal outcome improvement in HPV-positive metastatic non-oropharyngeal cancer patients due to small sample size. Future studies using larger cohorts must be done to address this issue. Even though the survival analysis was adjusted using clinical parameters including T, N, and treatments, we lack patient information on tobacco and alcohol consumption, which can also influence the analysis. Thus, we cannot exclude the potential biases from the heterogeneity of HPV testing methods, treatment order, smoking and alcohol status. Overall, HPV-positive mHNSC-OP patients had a more favorable outcome, particularly in patients with lung metastasis indicating that anatomy of primary and metastatic site are important factors to consider prior to treatment and clinical trial recruitment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Abbreviations:

HNSCC	head and neck squamous cell carcinoma
HPV	human papillomavirus
SEER	the Surveillance, Epidemiology and End Result database
mHNSC-P	metastatic HNSCC of pharynx
mHNSC-OP	metastatic HNSCC of oropharynx
mHNSC-non-OP	metastatic HNSCC of non-oropharynx
OPSCC	oropharyngeal squamous cell carcinoma

OS	overall survival
DSS	disease-specific survival
HR	hazard ratio
CI	confidence interval
MDSCs	myeloid-derived suppressor cells

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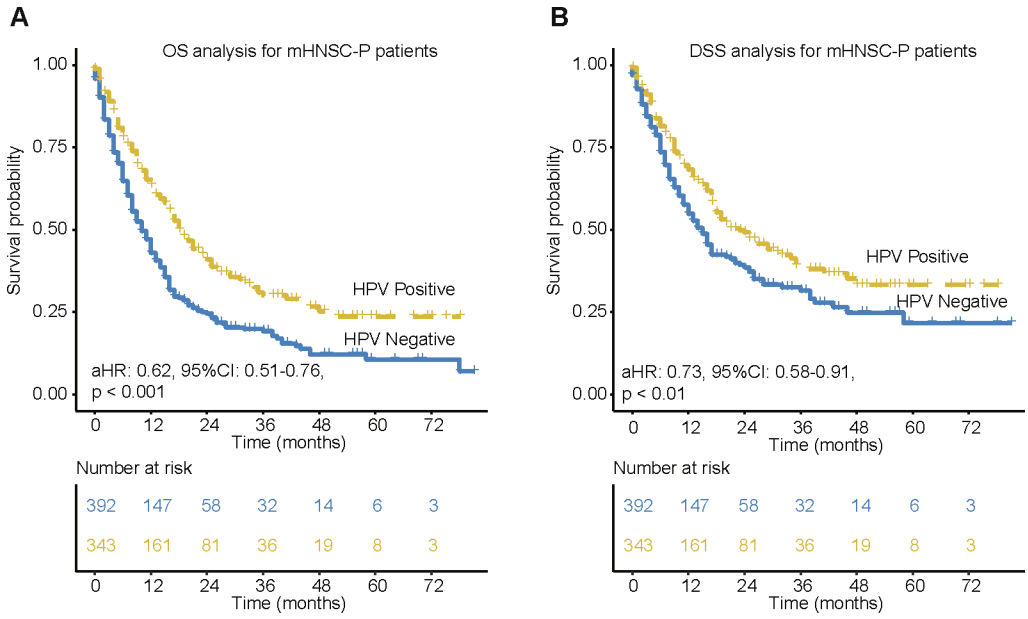

Fig. 1.

Kaplan-Meier of OS and DSS for metastatic head and neck cancer of pharynx patients. (A) OS based on HPV status in mHNSC-P patients. (B) DSS based on HPV status in mHNSC-P patients. aHR means Hazard ratio of HPV-positive vs. HPV-negative patients by adjusting for age, race, gender, grade, T stage, N stage and treatment. 95 %CI means the range of estimates with 95% confidence intervals.

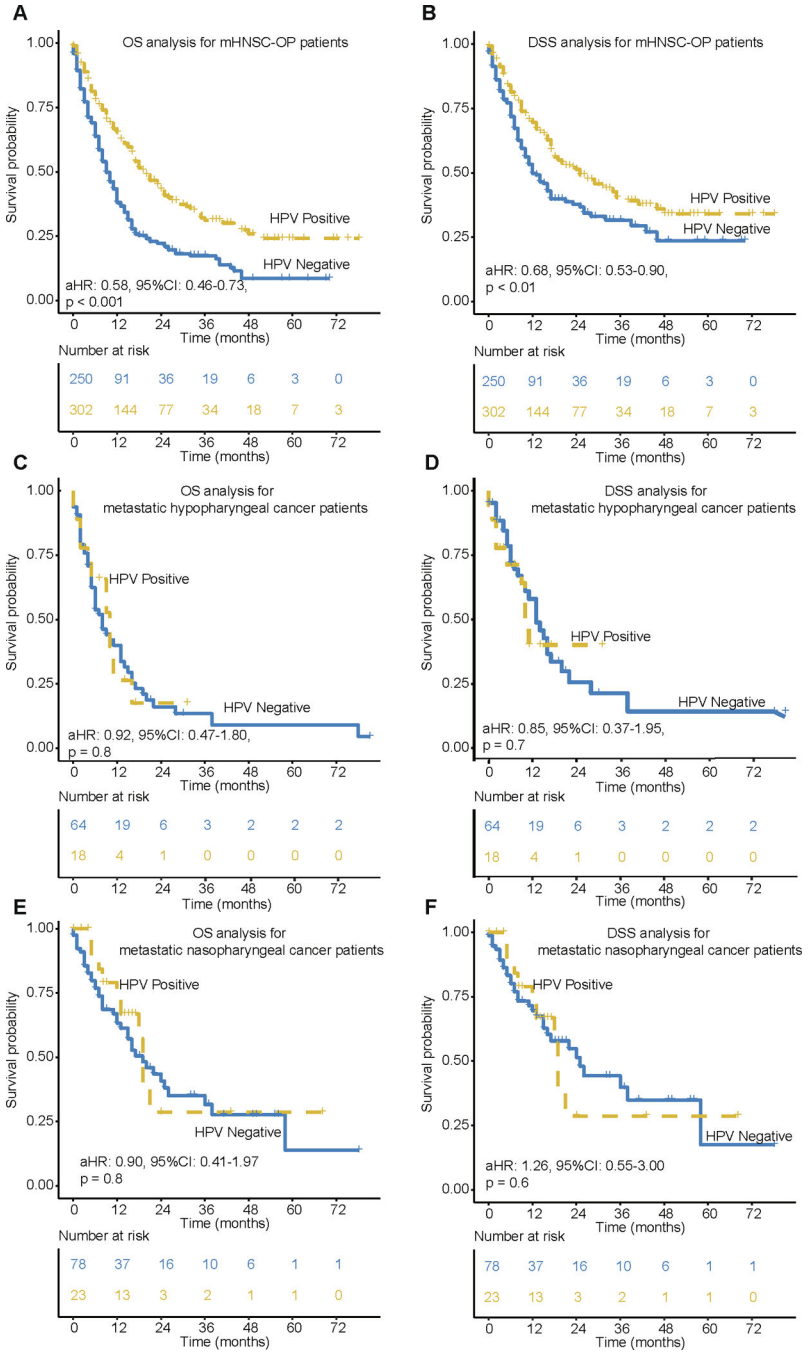

Fig. 2.

Kaplan-Meier of OS and DSS for mHNSC-OP and mHNSC-non-OP patients. (A-B) OS and DSS for metastatic oropharyngeal cancer patients by HPV status. (C-D) OS and DSS for metastatic nasopharyngeal cancer patients by HPV status. (E-F) OS and DSS for metastatic hypopharyngeal cancer patients by HPV status. aHR means Hazard ratio of HPV-positive vs. HPV-negative patients by adjusting for age, race, gender, grade, T stage, N stage and treatment. 95 %CI means the range of estimates with 95% confidence intervals.

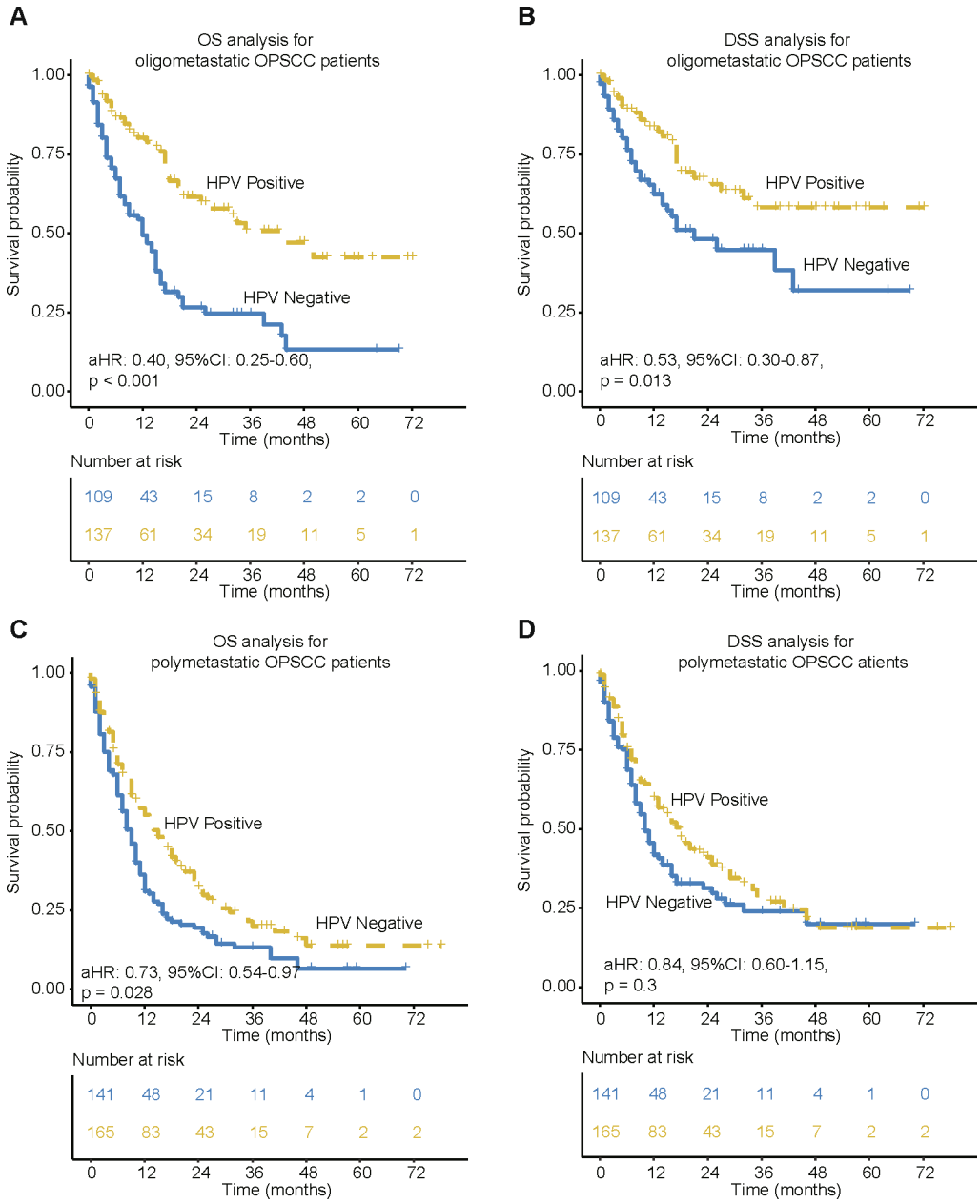

Fig. 3.

Kaplan-Meier of OS and DSS for mHNSC-OP patients with different numbers of distant metastatic sites. (A-B) OS and DSS for oligometastatic (only metastases in 1 site) mHNSC-OP patients by HPV status. (C-D) OS and DSS for ploymetastatic (>=2 sites) mHNSC-OP patients by HPV status. aHR means Hazard ratio of HPV-positive vs. HPV-negative patients by adjusting for age, race, gender, grade, T stage, N stage and treatment. 95 %CI means the range of estimates with 95% confidence intervals.

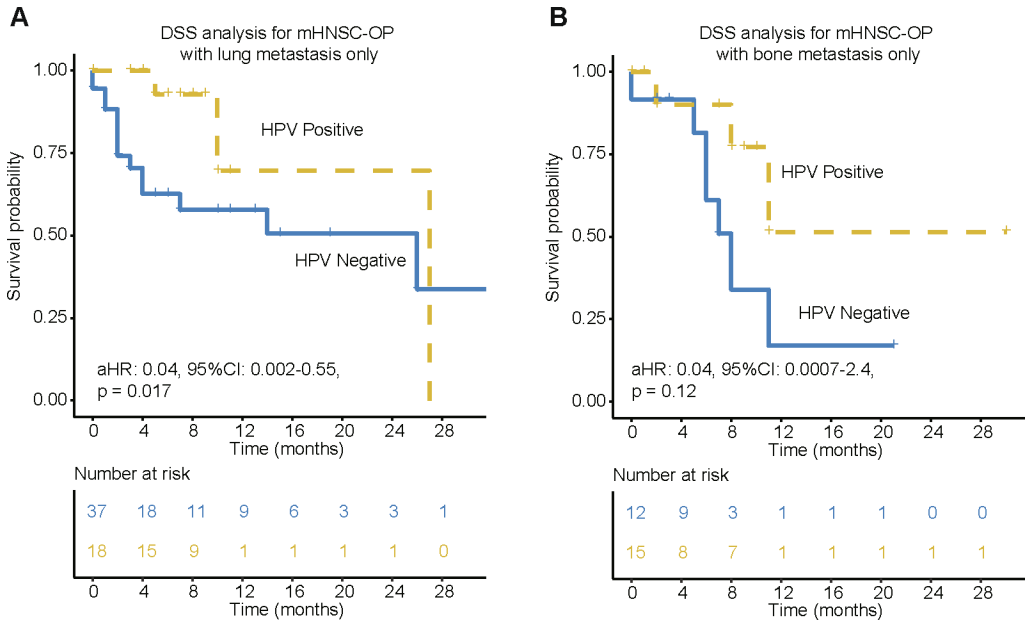

Fig. 4.

Kaplan-Meier of DSS for mHNSC-OP patients with lung or bone metastasis only. (A) DSS for HPV associated oligometastatic (only metastases in 1 site) mHNSC-OP patients with lung metastasis only. (B) DSS for HPV associated oligometastatic (only metastases in 1 site) mHNSC-OP patients with bone metastasis only. aHR means Hazard ratio of HPV-positive vs. HPV-negative patients by adjusting for age, race, gender, grade, T stage, N stage and treatment. 95 %CI means the range of estimates with 95% confidence intervals.

Table 1

Demographics and clinical characteristics for mHNSC-P patients.

Characteristic	HPV Negative N = 392[1]	HPV Positive N = 343[1]	p-value[2]
Age			> 0.9
<=62	201 (51%)	177 (52%)	
>62	191 (49%)	166 (47%)	
Sex			**0.011**
Female	91 (23%)	54 (16%)	
Male	301 (77%)	289 (84%)	
Race			**0.008**
Black	56 (14%)	38 (11%)	
White	276 (70%)	290 (85%)	
Others	60 (15%)	15 (4.4%)	
Primary site			**<0.001**
Non-Oropharynx Hypopharynx	64 (16%)	18 (5.2%)	
Nasopharynx	78 (20%)	23 (6.7%)	
Oropharynx	250 (64%)	302 (88%)	
Grade			**0.008**
I, II	123 (31%)	73 (21%)	
III, IV	153 (39%)	152 (44%)	
Unknown	116 (30%)	118 (34%)	
T stage			0.8
T1, T2	103 (26%)	96 (28%)	
T3, T4	154 (39%)	127 (37%)	
Unknown	135 (34%)	120 (35%)	
N stage			**<0.001**
N0, N1	105 (27%)	52 (15%)	
N2, N3	198 (51%)	203 (59%)	
Unknown	89 (23%)	88 (26%)	
Insurance			0.3
Insured	262 (67%)	251 (73%)	
Medicaid	98 (25%)	70 (20%)	
Uninsured	23 (5.9%)	16 (4.7%)	
Unknown	9 (2.3%)	6 (1.7%)	
Marriage			**0.003**
Married	158 (40%)	182 (53%)	
Separated	106 (27%)	62 (18%)	
Unmarried	105 (27%)	80 (23%)	
Unknown	23 (5.9%)	19 (6%)	
Treatment			**0.045**
Comprehensive Treatment [a]	210 (54%)	209 (61%)	

Characteristic	HPV Negative N = 392[1]	HPV Positive N = 343[1]	p-value[2]
Single treatment	116 (30%)	96 (28%)	
No/Unknown	66 (17%)	38 (11%)	
Bone			0.5
Yes	120 (31%)	98 (29%)	
No/Unknown	272 (69%)	245 (71%)	
Lung			0.06
Yes	197 (50.2%)	149 (43%)	
No/Unknown	195 (49.8%)	194 (57%)	
Liver			0.9
Yes	73 (19%)	61 (18%)	
No/Unknown	319 (81%)	273 (82%)	
Brain			0.02
Yes	23 (5.9%)	8 (2.3%)	
No/Unknown	369 (94.1%)	335 (97.7%)	
Number of metastatic sites			>0.5
1	163 (42%)	151 (44163%)	
>=2	229 (58%)	192 (56%)	

[1] n (%);

[2] Pearson's Chi-squared test;

[a] two or more than two treatments were given to patients such as chemotherapy plus radiotherapy.

Table 2

Hazard ratio for overall and disease specific death in HNSCC-DM patients by univariate Cox-proportional hazard model analysis.

Characteristic	Overall death		Disease specific death	
	HR[1] (95 %CI[2])	p-value	HR[1] (95 %CI[2])	p-value
Age				
<=62	Reference		Reference	
>62	1.07 (0.893–1.29)	0.448	0.909 (0.733–1.13)	0.382
Sex				
Male	Reference		Reference	
Female	1.07 (0.854–1.35)	0.546	0.937 (0.711–1.23)	0.644
Race				
White	Reference		Reference	
Black	1.06 (0.804–1.39)	0.691	1.01 (0.731–1.4)	0.938
Others	0.764 (0.548–1.06)	0.111	0.945 (0.664–1.35)	0.756
Primary site				
Hypopharynx	Reference		Reference	
Nasopharynx	0.471 (0.324–0.684)	**< 0.001**	0.604 (0.393–0.93)	**0.022**
Oropharynx	0.622 (0.474–0.816)	**< 0.001**	0.705 (0.507–0.982)	**0.038**
Grade				
I, II	Reference		Reference	
III, IV	0.737 (0.589–0.923)	**< 0.001**	0.782 (0.602–1.02)	0.065
Unknown	0.819 (0.644–1.04)	0.104	0.85 (0.642–1.12)	0.255
HPV status				
HPV Negative	Reference		Reference	
HPV Positive	0.594 (0.492–0.717)	**< 0.001**	0.698 (0.563–0.866)	**0.001**
T stage				
T1, T2	Reference		Reference	
T3, T4	1.37 (1.11–1.71)	**0.004**	1.36 (1.05–1.75)	0.019
Unknown	1.2 (0.927–1.56)	0.166	1.27 (0.944–1.71)	0.114
N stage				
N1, N2	Reference		Reference	
N2, N3	1.13 (0.905–1.4)	0.285	1.42 (1.09–1.85)	**0.0105**
Unknown	1.02 (0.719–1.43)	0.931	1.09 (0.716–1.66)	0.69
Insurance				
Insured	Reference		Reference	
Medicaid	1.18 (0.946–1.46)	0.144	1.2 (0.936–1.55)	0.148
Uninsured	1.39 (0.947–2.03)	0.0931	1.57 (1.03–2.39)	**0.036**
Unknown	0.89 (0.474–1.67)	0.717	1.1 (0.564–2.14)	0.783
Marriage				
Married	Reference		Reference	
Separated	1.63 (1.3–2.05)	**< 0.001**	1.32 (1 –1.73)	0.048

Characteristic	Overall death		Disease specific death	
	HR[1] (95 %CI[2])	p-value	HR[1] (95 %CI[2])	p-value
Unmarried	1.41 (1.12–1.78)	0.004	1.45 (1.12–1.88)	0.004
Unknown	1.14 (0.764–1.71)	0.513	1.04 (0.644–1.68)	0.875
Treatment				
Single treatment	Reference		Reference	
Comprehensive Therapy[a]	0.593 (0.48–0.733)	**< 0.001**	0.642 (0.501–0.823)	**< 0.001**
No/Unknown	3.35 (2.56–4.4)	**< 0.001**	3.58 (2.61–4.89)	**< 0.001**
Bone				
Yes	Reference		Reference	
No	0.642 (0.527–0.782)	**< 0.001**	0.552 (0.442–0.69)	**< 0.001**
Lung				
Yes	Reference		Reference	
No	0.761 (0.632–0.917)	**0.004**	0.702 (0.566–0.871)	**0.001**
Liver				
Yes	Reference		Reference	
No	0.796 (0.626–1.01)	0.062	0.702 (0.538–0.918)	**0.01**
Brain				
Yes	Reference		Reference	
No	0.559 (0.37–0.845)	**0.006**	0.494 (0.314–0.777)	**0.002**
Number of metastatic sites				
1	Reference		Reference	
>=2	0.91 (0.685–1.21)	0.517	0.862 (0.63–1.18)	0.355

[1] HR = Hazard Ratio;

[2] CI = Confidence Interval

[a] two or more than two treatments were given to patients such as chemotherapy plus radiotherapy